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Research Article

A COMPARISON OF SAFETY AND EFFICACY OF MIDAZOLAM AND MIDAZOLAM WITH FENTANYL FOR INTRAVENOUS SEDATION DURING MINOR ORAL SURGERY

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ABSTRACT

Aim of the study: Our aim was to compare patients' satisfaction and cooperation, and clinical efficacy, of midazolam alone, and midazolam and fentanyl citrate for intravenous sedation during day care minor oral surgical procedures.

Materials & methods: In this randomised, prospective study, forty patients who required day care minor oral surgical procedures were divided into two groups. In the first group, sedation was given with Midazolam and in the second group, combination of midazolam and fentanyl was given. Vital signs and oxygen saturation were recorded at every 5-minute interval during the procedure. Patients' and surgeons' satisfaction and the patients' degree of amnesia about the local anaesthetic, drilling, manipulation of soft tissues were also assessed by giving 2 questionnaires to patient and one to the operating surgeon.

Results: Results of this study showed that no significant differences, both statistically and clinically, between systolic and diastolic pressures, heart rate, oxygen saturation were found. Patient satisfaction and patient cooperation was more with the combination group ($p \leq 0.004$) than with the other group.

Conclusion: Intravenous sedation using the combination of midazolam & fentanyl is a safe and reliable technique to perform minor oral surgical procedures in a day care setting. Both patient and the operating surgeon comfort was significantly improved without altering the vital signs of the patient to extreme levels.

INTRODUCTION

Dental phobia is an important cause of avoidance of dental treatment. Many patients feel anxious before dental treatment on the presumption that the procedure will cause them pain and discomfort. Among dental procedures, oral surgery has been reported to induce the highest level of anxiety [17]. The successful management of fear and anxiety is a key to facilitated dental treatment in adult patients with severe odontophobia [18]. Even with all the modern advances in local anaesthesia, minor oral surgical procedures can cause pain and make patient uncomfortable. During some minor surgeries, the application of traction pressure and elevator forces can be unbearable by an apprehensive patient.

Conscious sedation is one of the tools of anaesthesia that reduces the anxiety of the patient during a painful minor dental procedure. Intravenous conscious sedation is the most popular method because of the ability to titrate drug accurately according to needs, rapid onset of action of the drug and more predictability in the action of drug. Drug dosage can be increased if further action is needed.

In our study, we divided patients into two groups receiving two different drug regimens. In one group of patients, a single drug regimen is used while in the other group, a combination of two drugs is used to achieve sedation. Among various drugs available, benzodiazepines are more commonly used for conscious sedation. Midazolam, a benzodiazepine, is the most preferred drug for conscious sedation by most anaesthesiologists. It has an ideal half-life suitable for its use in various minor oral surgical procedures. Clinical activity of the drug extends for about 45 minutes. Midazolam also produces anterograde amnesia [5] which is very valuable because patients do not remember the operative procedure, the pain and discomfort associated with it. This makes them receptive to future appointments.

Unfortunately, benzodiazepines do not have analgesic property which made many practitioners to search for an analgesic during conscious sedation[14]. Opioid analgesics are used in

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combination with benzodiazepines to induce analgesia during the procedure. In our study we used Fentanyl citrate, an opioid analgesic, to relieve pain during the procedure under conscious sedation using intravenous midazolam.

Fentanyl is a rapid-onset, short-acting opioid agonist that is approximately 100 times more potent than morphine [16]. Fentanyl does not cause hemodynamic alteration and it is indicated for patients with cardiovascular impairment. The main disadvantage of fentanyl is potent respiratory depression especially when combined with other sedative agents [15]. Many authors in the literature support the combination of an opioid and a benzodiazepine in conscious sedation and reported better patient comfort and cooperativeness in the combination regimen group than in the single regimen group without analgesic.

On the other hand, there are also a lot of reports in the literature discouraging the combination of opioid and benzodiazepine because of severe respiratory depression caused by the combination [3]. But some other studies state that if appropriate dosage of the two drugs is used the respiratory depression is not clinically significant [7], [2] ,[6].

Apart from this disadvantage, the combination therapy has many advantages like reduced operating time because the surgeon has the ease of working on the calm and cooperative patient and as a result better healing of tissues, decreased morbidity under minimal cost compared to general anesthesia and its associated morbidity. Thus it benefits both the patient and the surgeon.

The purpose of our study is to evaluate and compare the safety and efficacy of midazolam as an intravenous conscious sedative agent alone and when combined with fentanyl citrate in minor oral surgical procedures in dental office.

MATERIALS AND METHODS

The study sample consists of forty individuals who required minor oral surgical procedures in the day care setting. The sample is divided into two well matched groups each comprising of twenty patients. One group (Group A) received only midazolam during the procedure whereas the other group (Group B) received a combination of midazolam and fentanyl citrate. Patients were selected based on the anxiety level determined by the Corah's Modified dental anxiety scale [17]. The scale is in the form of a questionnaire which consists of four questions that evaluate patient's level of anxiety during routine dental procedures. Patient's level of anxiety is assessed based on the score derived by asking them to fill this simple questionnaire. The score can range from 4 to 20, with least score 4 denoting patient is not anxious while the highest score 20 denoting an extremely anxious patient. In our study, patients with a score of more than 12 were included.

All the patients were evaluated for their medical fitness. Only patients who were categorized as ASA 1 and ASA 2 were considered for our study. Exclusion criteria includes patients with a medical history of respiratory diseases like chronic obstructive pulmonary disease, bronchial asthma etc., and those patients who had a history of eventful conscious sedative procedures in the past and who were allergic to any of the sedative drugs. As per our Institutional review board and Ethical committee, informed consent for the study was mandatory for every patient.

Patient preparation for the procedure is same for both the groups. Patients were instructed to not to take any food or fluids orally eight hours prior to the procedure. They were also instructed to bring a responsible accompanying adult. Details of the procedure, risks of the sedation procedure, duration and recovery following the procedure were clearly explained to the patient and consent form was signed by the patient as well as the accompanying person on the day of the procedure.

The anaesthesiologist supervised the entire procedure and oversaw the titration of the drugs, infusion, maintenance and monitoring of the patient. Of the two groups of patients, one group was sedated using Midazolam (***Mezolam***®, Neon pharmaceuticals ltd) alone while the other group of patients received both Midazolam and Fentanyl citrate (***Verfen***®. Verve health care ltd.).

The dosage of the sedative drugs was titrated based on the patient body weight. The initial dose of midazolam administered, for both the groups, was 0.05mg/kg body weight at the rate of 1ml per minute to the loss of the eyelash reflex. The patient was observed for 2 minutes and if further administration was required, the drug was administered in 1 ml increments. The maximum permissible dose during the entire procedure was to be kept below 8mg. In group B, the dosage of fentanyl administered was 1mcg/kg body weight as bolus dose. There is no reduction in the dosage of midazolam in group B patients. Intravenous cannulas were used to access veins of the arm for the infusion of the drugs and are left in position for an easy access to give drugs in the case of any emergency event.

An emergency airway management kit comprising of oropharyngeal airways, ambu bags, laryngeal mask airways, a positive pressure oxygen delivery system, laryngoscope, various sizes of endotracheal tubes, a tracheostomy kit and an emergency drug cart were readily made available in the operating room. We made sure that antagonist drug to midazolam, ***Flumazenil*** was available within the emergency drug cart.

Various minor oral surgical procedures that require a day care setting were performed on the subjects in both the groups. These include removal of impacted third molars, incision & drainage of space infections, temporomandibular joint arthrocentesis, open reduction and internal fixation of uncomplicated mandibular symphysis fractures, enucleation of radicular cysts, incisional and excisional biopsies. The procedures were also matched in both the groups. All the procedures were performed by operators who were of same clinical expertise and were the senior residents in our institution. During the sedation procedure the operating surgeon was unaware of the group to which the patient belongs to.

An intravenous infusion of dextrose normal saline was started through the i.v.cannula. The titrated dosage of drug was then infused slowly until the loss of eyelash reflex. Then local anaesthetic agent (lignocaine hydrochloride with 1: 80,000 adrenaline) was injected to start the procedure.

Four parameters i.e., blood pressure, oxygen saturation levels, respiratory rate & pulse rate were monitored using a multi parameter patient monitoring device. (***L&T medical equipment, India***) continuously. Following the procedure, patients were shifted to the recovery room for one hour, after which they were evaluated and were given two questionnaires. One was for evaluation of the satisfaction of the patient regarding the procedure and the other for the measure of degree of amnesia. If the patient was alert and oriented, he or she was allowed to leave under the care of the accompanying person. Instructions regarding postoperative care and medication were given to the accompanying person.

Immediately after the procedure, the operating surgeon was given one questionnaire to subjectively evaluate the cooperativeness of the patient during the procedure. This operator questionnaire comprised of three questions regarding patient cooperation, movement during the procedure and verbalisation of discomfort with four choices per question. The first option carried a score of 1 signifying poor compliance and the fourth carried a score of 4 signifying excellent compliance. On summing up the scores of all the questions the minimum score is 3 and the maximum score is 12. Scores less than 6 were considered poor and scores above 10 were considered good.

The patient questionnaire to gauge satisfaction was similar in design to the operator questionnaire except that it had a total of four questions. The fourth question was to evaluate pain felt by the patient during the procedure. Correspondingly the lowest scores attainable were 4 and the highest scores were 16. Scores of 7 or lesser were considered poor while scores of 12 or above were considered good.

Lastly, the questionnaire to evaluate the degree of amnesia comprised of 8 questions related to the sequences of the procedure. For each question, a score of 1 depicted no recall of the event in question, and a score of 3 signified good memory of the event. The maximal achievable score was 24 and the minimum achievable score was 8.

RESULTS

In our study, forty patients, divided into two groups, were given fentanyl and midazolam combination (in Group A) and midazolam (in Group B) for achieving conscious sedation. Six parameters were evaluated between the two groups and results are as follows

Parameters evaluated were

1) Patient satisfaction
2) Patient Cooperation
3) Anterograde Amnesia
4) Heart rate
5) Blood pressure (systolic and diastolic),
6) Oxygen saturation.

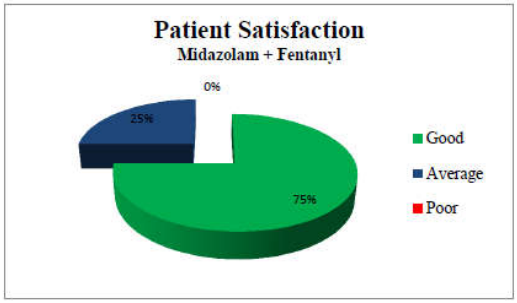
Of these, the first three parameters were non-quantitative and hence required Chi square test for evaluating significance whereas the next three were quantitative tests and required Anova test for evaluating the significance between the two groups.

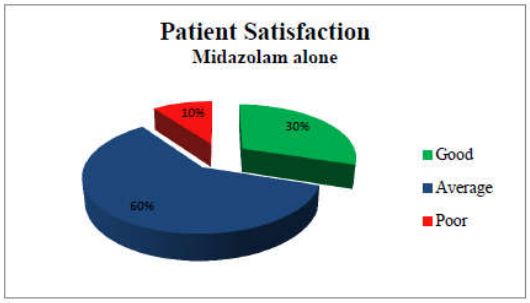
Patient satisfaction

On comparing the patient satisfaction scores between Group A and Group B, the mean scores obtained were 13.95 (SD: 2.578) and 11.00 (SD: 3.114) respectively. The mean difference between two groups was 2.95. Pearson Chi square test of equality of variance indicated that Group A or the combination group patients showed higher satisfaction compared to the other

Group ($p \leq 0.004$). When reviewed independently also, in group A 75% showed score indicating good level of satisfaction compared to 30% in group B. (Graph: 1)

Graph 1:





Patient Cooperation

This was measured based on the score obtained from the questionnaire given to the operating surgeon. Mean values between the two groups were 10.15 (group A) and 7.2 (group B) and their respective standard deviations were 2.12 and 2.92. Pearson Chi square test indicated that a significant difference in patient cooperation between the two groups was found. Group A patients were more cooperative compared to the group B ($p \leq 0.009$). Similarly, individual results showed 60% of group A patients showed good scores compared to 20% in group B patients. (Graph: 2)

Anterograde Amnesia

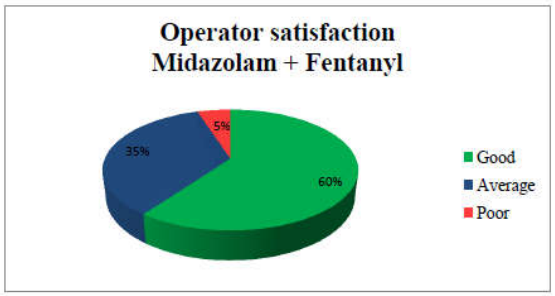
Chi square test showed no significant differences between Group A and Group B in amnesia scores. Both the groups reported similar score levels with p value 0.938. Individually in each group 45-50% of scores indicate average level of amnesia whereas 30% showed good level and 20% showed poor level of amnesia scores.

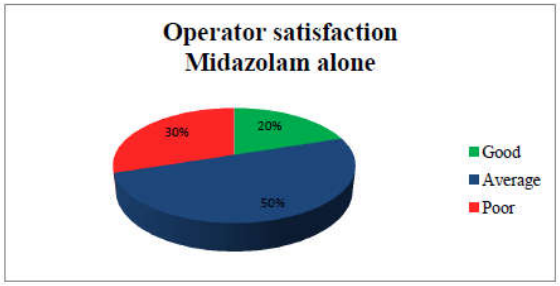
Oxygen saturation

The number of episodes of desaturation where oxygen saturation levels fell below 94% were counted and compared between the two groups. In midazolam only group (group B), there were 4 episodes of desaturation whereas as in the

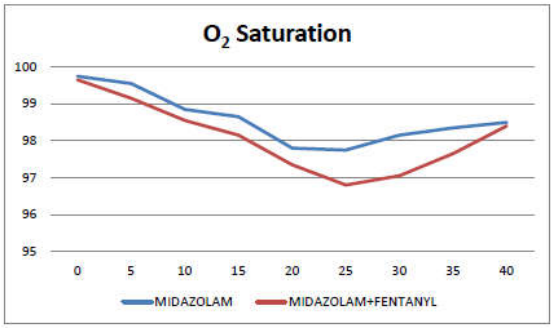
combination group (group A), there were 10 episodes. The frequency of the episodes of desaturation had no correlation with the body mass index and they happened to occur in the first twenty minutes from the commencement of the procedure. But the Kruskal- Wallis test performed to obtain significance indicated that this difference in desaturation episodes between the groups was not statistically significant ($p \leq 0.526$). Clinically these episodes were managed by rousing the patients and asking them to inhale deeply. Under no instance, a more aggressive management was required. (graph:3)

Graph 2:





Graph 3

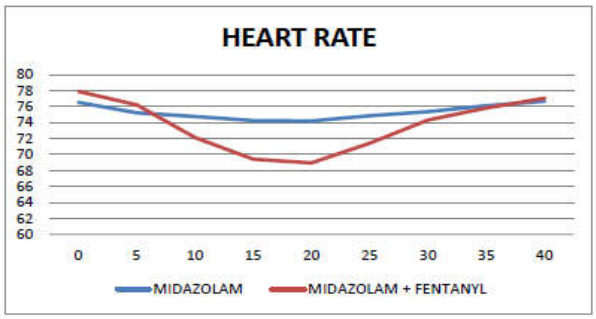


X-coordinates:- time in minutes Y-coordinates:- partial pressure of O_2

Heart rate

The mean scores of heart rate obtained in group A and group B were 73.67 and 75.31 respectively. And their respective standard deviation values were 3.27 and 3.55. The Anova test indicated that there was no significant difference present between the two groups ($p \leq 0.416$). Individual scores indicate that there was slight reduction of mean heart rate at 15- 20 minute time interval in Group A patients compared to the other group. But this reduction was not statistically or clinically significant. (graph:4)

Graph 4



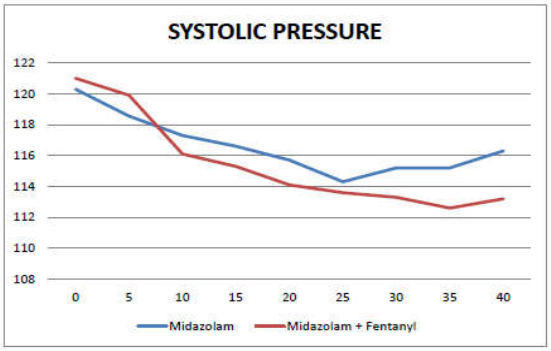
X-coordinates:- time in minutes Y-coordinates:- Heart rate

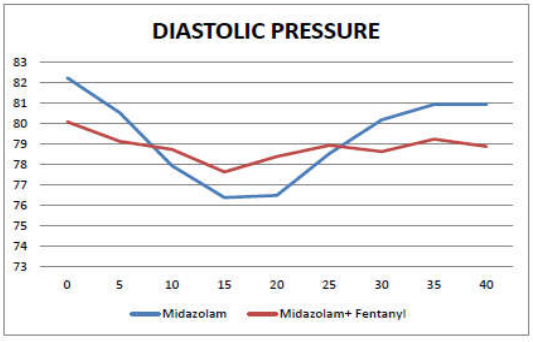
Blood pressure

On comparing the systolic and diastolic blood pressures between the two groups, the mean scores obtained were as follows:

Systolic pressures for group A and group B were 116.63 (S.D: 4.185) and 115.45 (S.D: 4.414) respectively. Similarly, the respective diastolic pressures for group A and group B were 78.86 (S.D: 2.817) and 79.36 (S.D: 3.914). The ANOVA test for both these parameters indicated that there was no statistically significant difference between the two groups in both systolic pressure ($p \leq 0.37$) and diastolic pressure values ($p \leq 0.51$). There was gradual decrease in the mean systolic pressure values in both the groups and in case of diastolic pressure values, Group B (midazolam only) showed decline in mean diastolic values up to 20 minutes and then increased to mean level. But this decline was not clinically or statistically significant. (graph:5)

Graph 5





X-coordinates:- time in minutes Y-coordinates:- pressure in mm Hg

DISCUSSION

Modern dental surgical treatment aims at improving patient comfort and pain control during the procedure. Various aids of anaesthesia are available for the surgeon to achieve this goal ranging from injection of local anaesthesia to general anaesthesia. Among these tools, conscious sedation plays a significant role in making the patient as well as the surgeon comfortable. As per ASA definition of conscious sedation, the drugs and/or techniques used should carry a margin of safety wide enough to render unintended loss of consciousness.

In our study, we performed various minor day care oral surgical procedures under sedation from 2012 to 2014. We aimed at the evaluation of safety and effectiveness of midazolam and fentanyl combination in conscious sedation. In the year 2005, a study was conducted in our institution regarding the role of midazolam in conscious sedation in minor oral surgical procedures.

In that study, the author reported that bodily movements of patients during the procedure due to pain caused difficulty for the operating surgeon. Hence surgeon satisfaction scores were reported low in the results of the study. We planned to do a similar kind of study by adding an analgesic sedative agent along with midazolam. We studied various parameters and compared them with the midazolam only group. These included patient satisfaction, operating surgeon satisfaction, degree of anterograde amnesia, blood pressure, heart rate and oxygen saturation.

Intravenous sedation is an effective and popular method used for reducing anxiety in patients. Midazolam is widely used as a sedative agent. Its amnesic property has been used during the procedure so that the patient, who may be awake and responsive during the surgery perceives that he or she was asleep throughout the surgery.

Though midazolam has better sedative and amnesic properties, its lack of analgesic property can cause discomfort to the patient during manipulation of soft tissues, tractional forces applied during the surgical procedure even though local anaesthesia has been administered at the site of surgery (Parworth *et al*.) [12]. This can be an important factor in some short painful procedures for example temporomandibular joint lavage, fracture reduction etc. We have chosen fentanyl citrate as the analgesic agent in our study because of its potent analgesic property, its short half-life and its ease of administration.

According to The American Dental Association guidelines [1] for administering moderate anaesthesia for minor oral surgery, monitoring of level of consciousness, oxygenation, ventilation, blood pressure, and heart rate was mandatory. In addition to these parameters, satisfaction levels of patient and operator were also included in our study.

Among the two groups of patients, we evaluated patient satisfaction, patient cooperativeness during the sedation procedure by giving questionnaire both to the patient and the operating surgeon. Other parameters were recorded during the procedure continuously.

Regarding the operating surgeon satisfaction or patient cooperation, we found significant differences between the two groups ($p \leq 0.009$). To avoid bias in the results, the operating surgeon was blinded by not revealing to which group the patient belonged to. The operating surgeon's satisfaction was excellent in the combination drug group compared to the other group. In painful procedures like reduction of symphysis fracture of mandible, TMJ arthrocentesis, the adequate relief of pain to the patient was found in the combination group due to the effective analgesic action of fentanyl administered. The bodily movements of the patient were also reported to be minimal.

Similarly regarding patient satisfaction, patients in the combination group were more satisfied compared to the midazolam alone group ($p \leq 0.004$). This might be because of additional pain relief provided by fentanyl in the combination group patients. Patient attitude towards the procedure also improved significantly. Similar results were shown by Hasan *et al* in 2007 [9]. They showed that the combination of midazolam with a drug of the opioid group was more beneficial compared to midazolam without opioid group.

Other parameters included in the comparison were heart rate, blood pressure and oxygen saturation levels during the procedure. Heart rate was slightly reduced during the procedure in both the groups but we did not observe any clinically significant difference ($p \leq 0.416$) in the reduction of the heart rate. Our results can be compared with the results of other investigators. Rodrigo and Fung in 1999 [13] concluded that there is no statistical difference in reduction of heart rate. Similarly, Hasan G. *et al* (2007) [10] reported that heart rate after 30 min in the combined group was lower than in the midazolam group. But this reduction was not clinically significant. The reduction of heart rate might be physiologically related to inhibition in vasomotor centre in medulla oblongata of brain and due to stimulation of vagal tone by both the drugs.

Compared to preoperative values, the blood pressure was reduced in both groups, which was to be expected after sedation with midazolam and fentanyl. There was reduction in both systolic and diastolic pressures. The decrease was not statistically significant and it has no clinical importance. Hasan G. *et al* (2007) [10] reported that there were no significant differences between systolic and diastolic blood pressures during sedation. Similar findings were given by Esen *et al* [6] and Gold *et al*. [8] Reduction of blood pressure both systolic and diastolic can be attributed to the direct action of drugs in decreasing tone of blood vessels and decrease in the peripheral resistance by the midazolam.

Various articles in literature report that the common side effect of benzodiazepine and narcotic analgesics is respiratory depression.[2],[3],[15] Bailey *et al* (1990) [3] reported that combination of midazolam and fentanyl was reported to produce clinically significant intraoperative respiratory depression. Similarly, in our study episodes with decreased oxygen saturation below 94% was observed in some cases. Physiological cause of reduction in the respiration might be due to neurogenic, hypercapnic and hypoxic drives to respiratory centre in medulla oblongata being depressed by both midazolam and fentanyl together. During these episodes, we stopped the procedure and the patient was supplied with external oxygen and was asked to inhale deeply. Even though

emergency airway kit was made readily available, we did not use them because these desaturations were reversed by giving verbal commands to the patient to take a deep breath. None of our patients in both the groups required additional airway manoeuvre or intubation. These results can be compared to that of Ganzberg *et al*,[7] Avramov *et al*,[2] and Esen *et al*,[6] who reported that narcotics increased respiratory depression when combined with midazolam; however, using appropriate doses it will not cause a clinically important depression.

We also assessed the degree of anterograde amnesia of midazolam in an objective way by asking the patient to fill in the questionnaire regarding the steps in the procedure. The cause of anterograde amnesia due to midazolam is due to inhibition of Hippocampus region of the brain. Interestingly, patients did not recall the steps done during the initial 25- 30 minutes of the procedure as reported by Bell & Kelly in 2000 [4], [11]. So we tried to perform the main course of the procedure during this period where extreme painful events might be experienced by the patients. Both the groups showed similar levels of amnesia without any significant difference.

In our study we tried to achieve both patient and operating surgeon satisfaction during the procedure along with maintaining the physiologic parameters of the patient within the normal range. We did not encounter any major disadvantage by combining midazolam and fentanyl like respiratory depression or chest wall rigidity by titrating dosages for every patient individually.

Conscious sedation has been used widely in day-care surgical procedures in both dental and medical fields in developed countries. But in India the role of conscious sedation in dental surgery is not so popular. The reason could be the lack of knowledge regarding the technique. Compared to general anaesthesia, conscious sedation is cost effective and safe to the patient. It does not include extensive armamentarium and costly materials to provide
sedation to the patient.

We kept a Boyle's apparatus readily available following prescribed safety norms. Its use was not required in anyone of our patients in any circumstances. In our study, we used a multiparameter monitor even though as per American Dental Association guidelines [1] a clip –on variety pulse oximeter is adequate. The individual costs of both the drugs were cost effective and affordable by our patients. Thus providing conscious sedation in dental office setting can be effectively managed if effective dosage of drugs is carefully titrated and administered without any serious effects.

SUMMARY AND CONCLUSION

Intravenous conscious sedation using Midazolam and fentanyl citrate is a safe and efficient way to reduce anxiety and fear of pain in patients who require minor day care surgical procedures. Patient as well as operator comfort during the procedure is high and at the same time maintaining vital parameters of the patient within normal range during the procedure. Efficient titration of dosage of drugs for individual patient is crucial to achieve these results. Further studies with a larger sample size might be carried out to support our results.

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